PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference P02/087-bzgs	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06055	International filing date *(day/month/year)* 10.06.2003	Priority date *(day/month/year)* 11.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K47/48		
Applicant MERCK PATENT GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.12.2003	08.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Turri, M Telephone No. +49 89 2399-7712

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06055

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-43 as originally filed

Claims, Numbers

1-16 as originally filed

Drawings, Sheets

1/13-13/13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

The examination is being carried out on the **following application documents:**

Text for the Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR

Description, pages:

1-43 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/13-13/13 as originally filed

1. General remarks

1.1 Reference is made to the following documents:

D1: WO 00 34317 A (ADAIR FIONA SUZANNE ;CARR FRANCIS JOSEPH (GB); HAMILTON ANITA ANNE) 15 June 2000 (2000-06-15) cited in the application

D2: WO 98 52976 A (BIOVATION LTD ;CARR FRANCIS J (GB)) 26 November 1998 (1998-11-26)

2. Novelty

2.1 Document D1 discloses an altered bryodin 1 sequence (Figure 10), where 10 amino acids have been modified, being non-immunogenic or less immunogenic as compared to the wild-type bryodin 1.The modified bryodin 1 is considered as novelty-destroying for claim 1 (**Article 33(2) PCT**).

3. Inventive step

3.1 Document D2 discloses a method to render proteins, or part of proteins, non-immunogenic or less immunogenic, to a given species by identifying in their amino acid sequences one or more potential epitopes for T-cells of the given species and modifying the amino acid sequence to eliminate at least one of the T-cell epitopes.

3.2 Document D1 cites document D2 as a relevant piece of prior art (see page 2, line 28), and discloses the application of said method to bryodin 1.

3.3 However, although epitopes in a protein can be predicted and modified with computer methods, it is considered that a certain level of experimentation is required to ensure that they actually work. An inventive step can therefore only be recognized for epitopes (peptides) that have been experimentally tested as stimulating an immun. response or as non- or less immunogenic after modification.

3.4 In the present application, 85 synthetic peptides (15mers) that overlapped by 12 amino acids were generated that spanned the entire sequence of bryodin 1.Their identification numbers and sequences are given in Figure 2. They correspond to SEQ ID NOs:100-184.

3.5 This peptides have been used to measure the stimulation of T-cell proliferation. The results are shown in Figure 4. As indicated above, peptides shown there as inducing a positive response are considered to involve an inventive step (**Article 33(3) PCT**).

3.6 The present set of claims, however, is not directed to said peptides. The claims are directed to a bryodin molecule non- or less immunogenic as the wild type bryodin, wherein the loss of immunogenicity is obtained by removing one or more T-cell epitopes.

3.7 In claim 3, the epitopes are selected from the sequences of Figure 1, corresponding to SEQ ID NOs:11-99. They are 13mers with *potential* human MHC classII binding activity. This peptides, however, have never been tested experimentally as epitopes.

3.8 Similarly, in claims 4 and 5 the epitopes are selected from peptides within or corresponding to the R1-R5 sequences. Also in this case, no experimental data support the fact that R1-R5 peptides act as epitopes.

3.9 Also, there is no indication in the application of which sequences have been actually used in Figures 6-10. It is only said that they were identified using the in silico method

of Example 1. Since the sequences are not given; it is not possible to determine which modified bryodin sequences as in claim 9 have been ever used in the experiments of Figures 6-10.

3.10 Present claims 2-16 are therefore not considered to involve an inventive step (**Article 33(3) PCT**).

4. Unity (Rules 13.1 and 13.2 PCT).

4.1 This Authority considers that there are many inventions covered by the claims. The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by **Rule 13.1 PCT**, are as follows:

4.2 the subject-matter of claim 1 is not considered to be novel (see above), and is therefore devoid of special technical features within the meaning of **Rule 13.2 PCT**;

4.3 Also, since for the peptides identified by SEQ ID Nos:11-99 and R1-R5 (claims 2-10) it doesn't seem possible to identify a corresponding technical effect as well, there is no single general inventive concept for the cited peptides, and therefore each of them define a different invention.

4.4 Hence, he application does not meet the requirements of unity of invention as defined in **Rules 13.1 and 13.2 PCT**.